modulate antigenicity and receptor binding, confounds retrospective analysis of genetic variation in HA. The situation is complicated further by the occurrence of epistatic changes within HA and between HA and NA to maximizeviral fitness following selection. Moreover, substitutions selected to modulate receptor avidity will inevitably modify receptor specificity for various sialic acid terminated-glycans and vice versa. From leaves to forest: even in the simplest species (viruses), evolution is complicated, and oversimplified analysis leads to all sorts of errors, including those with practical ramifications in interpreting sequences for choosing vaccine strains.

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Lessons Learnt from (HIN1)2009 Influenza Pandemic for Preparedness Against Future Pandemics

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Pandemic (H1N1) 2009 was relatively mild with less severe disease burdens and social impact. Pandemic (H1N1)pdm09 virus itself was low pathogenic, similar to seasonal flu viruses and different from H5N1 highly pathogenic avian influenza viruses. Most people had acquired immunity to Spanish flu or former seasonal H1N1 flu viruses, which was cross-protective, in part, against H1N1pdm09 virus. The pandemic started in the North America, where US CDC detected and identified the causative virus rapidly, sharing information with WHO to take immediate responses. Most countries had been prepared, more or less, against a possible pandemic by H5N1. H1N1pdm09 virus hardly underwent antigenic drift and the pandemic vaccine remained matched and effective. The virus was susceptible to neuraminidase inhibitors and drug-resistant viruses did not spread, unlike former seasonal H1N1 virus during 2007-2009. The pandemic virus did not increase the pathogenicity, unlike Spanish flu in 1918/19. Finally, disease burdens and social impact remained far below previous assumptions against a possible H5N1 pandemic. On the other hand, pandemic vaccine production and supply were delayed and insufficient and much confusion occurred due to misleading by health authorities and media. It appeared clear that implementation of pandemic preparedness plans had been suboptimal in many settings.
During the pandemic (H1N1)2009, H5N1 highly pathogenic avian influenza continued to spread in several areas causing human infections. WHO is keeping its pandemic alert level Phase 3. Both H1N1pdm09 and H5N1 viruses were shown to infect pigs in China and Indonesia and therefore, gene reassortment between the viruses may occur in pigs or humans. Risk of an H5 pandemic still remains or is increasing, which will cause extremely heavy disease burdens and social disruptions.
We should also learn much from the devastating earthquakes and tsunami and the resultant nuclear power plant accident, which occurred at much severer levels far beyond the government's "optimistic assumptions", bases for the suboptimal preparedness. The worst thing we can do is not prepare for a worst case scenario and think it will not happen. We must be prepared against a worst-case scenario of pandemic influenza caused by a highly pathogenic virus.

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Strategies for Control of Pandemic Influenza: Active and Passive Immunization

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Pandemic influenza poses a serious threat to global health and the world economy. Highly pathogenic avian influenza A virus (HPAIV) of the H5N1 subtype that has emerged since 2004, resulted in more than 430 cases in 15 countries with a 50% case-fatality rate. Novel vaccine strategies for early response include the use of attenuated vaccines/vectors administered via novel mucosal immunization routes, therapeutic anti-virals and passive immunization with virus-specific antibodies (Abs).
The current influenza vaccines designed for inducing antibody (Ab) responses against viral surface antigens (i.e., hemagglutinin [HA] and neuraminidase [NA]) are limited to seasonal use because of the ability of the virus to mutate these major antigenic glycoproteins. Vaccines that target determinants conserved among influenza A viruses (IAV) to generate broad protection against infection with different influenza A subtypes (i.e., heterosubtypic immunity [HSI]) remain elusive. We have currently developed a recombinant adenovirus (Ad) vector co-encoding HA (H5 subtype) and a conserved ectodomain of matrix protein 2 (M2e) (AdH5/M2e) for induction of protective immunity to H5N1 and other subtypes. Another approach based on the use of influenza virus carrying a deletion in the nonstructural NS1 gene is being explored. Since NS1 enables the virus to disarm the host type 1 IFN response, such deletion leads to attenuation of the viruses and enhanced host antiviral response. Therefore, vaccines based on NS1 deleted viruses (DelNS1) may provide better protection than inactivated vaccines and could induce HSI to infection with different influenza virus A subtypes. Sub-lingual immunization has been found to be a safe and effective route for induction of protective immune responses in systemic and mucosal compartments including respiratory tract. We found that sublingual immunization with either AdH5/M2e or DelNS1 induces broad protective immunity to H5 viruses and other influenza virus A subtypes including H1N1.
Passive immunization (the transfer of specific immunoglobulins/Abs to a previously nonimmune recipient host) could offer an alternative strategy to prevent and treat influenza virus infection and an additional therapeutic option to antiviral drugs that are limited by widespread drug resistance among influenza virus strains. Even after targeted vaccines become available, passive immunization could still have prophylactic effects and provides an additional countermeasure against influenza, especially for individuals who do not respond well to the vaccines. Attempts to develop monoclonal Abs (mAbs) have been made. However, passive immunization based on mAbs may require a cocktail of mAbs with broader specificity in order to provide full protection since mAbs are generally specific for single epitopes. Because the recent epidemic of highly pathogenic avian

influenza virus (HPAIV) strain H5N1 has resulted in serious economic losses to the poultry industry, many countries including Vietnam have introduced mass vaccination of poultry with H5N1 virus vaccines. We found that eggs obtained from chicken farms and supermarkets in Vietnam contain H5N1-specific immunoglobulins (IgY) that provide protection against infections with HPAIV H5N1 and related H5N2 strains in mice. When administered intranasally before or after lethal infection with HPAIV H5N1, H5N1-specific IgY prevent disease or significantly reduce viral replication resulting in complete recovery from the disease, respectively. In addition, we generated H1N1 virusspecific IgY by immunization of hens with inactivated H1N1 A/PR/8/34 as a model virus for current pandemic H1N1/09 and found that such H1N1-specific IgY protect mice from lethal influenza virus infection.

These results underscore the usefulness of recombinant Ad vectors encoding surface glycoprotein (HA) and conserved protein (M2e) and NS1 deleted viruses (DelNS1) as vaccine candidates for control of pre-pandemic H5N1 and newly emerging subtypes. Data on antiviral efficacy of IgY provide a proof-of-concept for the approach using virus-specific IgY as affordable, safe, and effective alternative for the control of influenza outbreaks, including the potential H5N1 and current H1N1 pandemic.

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From Lessons Learned After 2009 H1N1 Pandemic to TEPIK's Preparedness and Response Plan

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In response to the global spread of the H1N1 influenza virus after first being detected in North America in April 2009, WHO declared the first influenza pandemic in more than four decades on June 11 of the same year. In Korea, the arrival of the 2009 H1N1 pandemic influenza triggered an integrated response that was mainly based on the 2006 Pandemic Influenza Preparedness and Response Plan. At least 270 fatal cases, 764 laboratory-thousand confirmed cases, and 3.6 million courses of antiviral agent use were reported to the end of August 2010 in this country. Even if government tried to control and mitigate the impact of pandemic by using public health and medical countermeasures, there were several issues found during the H1N1 pandemic responses. The main difficulty was the delayed and insufficient supply of pandemic vaccine. Therefore the mass vaccination campaign was begun after the peak of pandemic and its mitigation effect on the pandemic disease burden was diminished. The amount of stockpiled antiviral agents by government was not enough in the early phase of pandemic. The rapid antigen test for the H1N1 influenza showed low sensitivity, about 50%. Many infected people were seeking to be diagnosed with rRT-PCR test, which is expensive and not useful for the decision of antiviral use because of late test report. The communications among government, medical societies, general people and mass media were also not satisfactory. Lessons learned from the national response to the H1N1 pandemic made the government to launch the TEPIK in October 2010. TEPIK will incorporate those lessons into the future pandemic preparedness planning. The mission of TEPIK is to ensure the safety of the nation and people from the threat of pandemic influenza. TEPIK focuses to establish government-academic-institute-industry collaborative system with three main strategies; to expedite sharing of R&D information and preparation of national communication; to establish the preparedness and response of R&D investment strategy for usual and pandemic phase; and to secure the innovative and leading response technology against pandemic influenza. TEPIK has 34 research projects in eight research areas, which include vaccine; therapeutics; diagnostics; basic/mechanism; clinical/policy; surveillance/epidemiology; innovative researches; and infrastructures. Research subjects in each research area will be stated in this presentation.

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Perspective of Influenza Research in Korea NIH

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Until 2000 when the Communicable Diseases Control Law was revised, influenza has been considered as one of the neglected disease in Korea. The vaccine coverage was low and there were no reliable statistics about influenza. With the revision of the Law, influenza was grouped as group III disease which needs surveillance and Korea Influenza Surveillance Scheme (KISS) was launched on September of 2000.

While the surveillance system has been established and improved with following seasons, diagnosis and related research has been diversified and intensified. With the successive outbreak of SARS and avian influenza outbreaks from 2003, 2006, 2008 and 2010, diagnosis of influenza has been improved by the introduction of genetic detection from RT-PCR to multiplex RT-PCR. During the 2009 pandemic we introduced the multiplex realtime RT-PCR and it is being used now which can differentiate seasonal influenza (H1, H3 and B), A(H1N1)pdm09, and H5. For the serological diagnosis, conventional hemagglutination inhibition and microneutralization has been established with standardization for each virus using various red blood cell or variation of HA antigen preparation. Also to minimize the possible infection by highly pathogenic avian influenza virus (HPAIV), microneutralization using pseudotype virus with appropriate HA gene of HPAIV has been developed.

Also with the increased the need for molecular analysis based on sequence, Influenza Sequence and Epitope Database (ISED) was developed in 2008 and expanded the contents from seasonal influenza to avian influenza with various hosts. The result of genetic characterization to detect the variation in antigenic sites and antiviral drugs resistance has been widely used for the surveillance and also for the treatment of influenza patients since the worldwide spread of drug resistant virus.